REMARKS

Receipt of the Office Action mailed February 23, 2010 is hereby acknowledged. Reconsideration of the rejections in view of the foregoing amendments and the following remarks is respectfully requested.

Amendments

Claim 57 has been amended to more particularly point out that the large neutral amino acid (LNAA) supplement comprises, as the sole amino acid ingredients, Tyr, Trp, Met, iLeu, Thr, Val, Leu, and Lys, and optionally Arg and His. Thus, the supplement according to the invention contains each of Tyr, Trp, Met, iLeu, Thr, Val, Leu, and Lys, and can optionally contain Arg and/or His. No other amino acids are in the claimed supplement, although other additives can be present. The supplement is substantially free of phenylalanine. Lys is present in an amount of 5 to 30 mg per 500 mg of total supplement (i.e. the amino acids plus any other additives), and the weight ratio of Leu:iLeu is greater than 1:2, as is the weight ratio of Leu:Val. The amount of Lys is supported in the specification at page 13, lines 32-33. Claim 60 has been

amended to recite that the upper limit of Lys is 20 mg per 500 mg of supplement. This amendment is supported in the specification at page 31 in Table 5 (SuppM2). Claim 69 has been amended to recite that the upper limit for Lys is 30 mg per 500 mg of supplement.

Claim Objections

The Examiner objected to claims 57-70 because the acronym LNAA was used without ever using the full term. Applicant has followed the Examiner's advice and used the full term ("large neutral amino acid") in independent claim 57, with the acronym "LNAA" following in parentheses. This amendment should obviate the objection.

Rejection under § 112

The Examiner rejected claims 57-70 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite on the grounds that "it [was] unclear whether the claimed 'sole amino acid ingredients' refers to the optional Arg and His or the other amino acids listed in the claim." Applicant submits that the amended claim makes clear that the only amino acids present are Tyr, Trp, Met, iLeu, Thr, Val, Leu, and Lys, and

optionally Arg and/or His. No other amino acids are present. Thus, Applicant submits that this rejection has been obviated.

The Examiner has also asserted that the phrase "the weight ratio of Leu to iLeu is greater than 1:2, and the weight ratio of Leu to Val is greater than 1:2" is indefinite because "one of skill in the art would not be able to determine what [A]pplicant means by a greater than 1:2 ratio..." Applicant respectfully traverses.

As noted above, claim 57 requires that the weight ratio of Leu to iLeu be "greater than 1:2." A person of skill in the art would clearly understand that a weight ratio of "greater than 1:2 means that the weight of Leu has to be greater than 50% of the weight of iLeu. If the weight of Leu is not greater than 50% of the weight of iLeu, then the weight ratio of Leu to iLeu is not "greater than 1:2."

In response to the Examiner's specific question ("Is a 1:1 ratio greater than 1:2 ratio because there is more Leu even though it's a smaller ratio?"), a 1:1 ratio is a greater ratio (equal to 1) than a 1:2 ratio (equal to 0.5). Applicant also notes that the Examiner appears to have properly interpreted the claim in making the anticipation rejection at page 5 of the Office Action.

In view of the foregoing, Applicant respectfully submits that this language is clearly definite within the meaning of 35 U.S.C. § 112, second paragraph, and requests reconsideration and withdrawal of this rejection.

Anticipation Rejection

The Examiner rejected claims 57, 61, 63, and 65 under 35 U.S.C. § 102(b) as allegedly anticipated by Wachtel, et al., DE 4037447 ("Wachtel"). The Examiner points to the formulation set forth in claim 4 of Wachtel at pages 16-17 of the translation, converts to weight percentages to a ranges based on a 500 mg sample, and arrives at the following composition:

Amino Acid	Wachtel (mg/500 mg)
Tyr	72-88
Trp	14.4-21.6
Met	19.6-29.4
iLeu	53.6-65.5
Thr	38-57
Val	64.8-79.2
Leu	90.9-111.1
His	20-30
Lys	65.3-79.8

According to the Examiner, this formulation anticipates claim 57. Applicant traverses.

Even if the foregoing numbers are taken at face value, they recite an Lys-content of between 65.3 and 79.8 mg/500 mg,

which is outside the scope of the present claims (which recite an upper limit of 30 mg of Lys per 500 mg of supplement). Thus, claim 57 cannot be anticipated by Wachtel. Nor can any of the other rejected claims, each of which depends from claim 57, be anticipated either. Therefore, Applicant respectfully requests withdrawal of the anticipation rejection.

Obviousness Rejection

The Examiner has rejected claims 58-60, 62, 64, and 66-70 under 35 U.S.C. § 103(a) as allegedly unpatentable over Wachtel. The Examiner asserts that it would have been a matter of routine experimentation to modify the amount of lysine to arrive at the presently claimed composition. According to the Examiner, Wachtel teaches that proportions of the individual amino acids may vary depending on the individual's metabolism, and the Examiner contends that a difference of 15 or 35 mg (of lysine) is not outside the limits of routine optimization. Applicant traverses.

Applicant respectfully submits that the Examiner has not fully appreciated the core of the presently claimed invention, which is not simply a result of finding the optimum percentages of lysine in an "already generally known"

supplement. The Examiner is mistaken in stating that "the applicant has modified the dosage of one amino acid *(lysine)* slightly but has not demonstrated that this modification would produce any unexpected results or that one of ordinary skill in the art would not consider adjusting the dosage of any amino acid by such small amounts for each individual's needs."

The Examiner appears to believe that the present invention is simply a refinement of the product disclosed by Wachtel. This is a misconception. Wachtel is concerned with an improved treatment of phenylketonuria (PKU) in juvenile to adult patients. However, Wachtel is not directed the specific problem that is intended to be solved by the present invention.

The two solutions to the treatment of PKU (the LNAA supplement of the present invention and the phenylalanine-free diet of Wachtel) may appear at first glance to have some similarities, but a person of skill in the art would immediately recognize that they are very different.

Wachtel is directed to a phenylalanine-free diet based on amino acids for persons afflicted with PKU, in particular for juveniles and adults, where the amino acid residues His, iLeu, Val, Thr, Met, Leu, Trp, Tyr and Lys constitute at least 95% of the total amount of amino acids in the diet. However, because

the diet must fulfill the patient's nutritional requirement for amino acids, it must reflect both absolute and relative amounts in the diet, as shown in claim 4 of Wachtel. Prior to Wachtel, the belief in the art was protein metabolism requires simultaneous presence of all essential and non-essential amino acids. They usually used products or Phe-free amino acid mixtures for babies and children which contained all the amino acids with the exception of Phe.

A considerable amount of these substances were necessary to cover the patient's daily needs. By adolescence, however, the treatment requirements of PKU were often refused by the patient, even though experts suggested that they maintain the Phe poor diet for life.

Thus, Wachtel sought to prepare a Phe-free diet or a Phe-free amino acid mixture, which was more acceptable to *patients* suffering from PKU and promoted a *life-long intake* of *diet.* Wachtel's solution was to provide a diet composition that may cover completely or almost completely the daily protein (amino acid) requirement of juveniles and adults suffering from PKU with an amino acid mixture which contains predominantly or exclusively essential amino acids with the exception of Phe, as well as Tyr and His. Wachtel's composition was different

from prior diets, which contained all amino acids, both essential and non-essential, except Phe.

Wachtel taught that a diet containing only the essential amino acids, would stimulate the body into synthesizing the non-essential amino acids, permitting a reduction in the amount of the composition which needed to be ingested. Thus, Wachtel disclosed that patients suffering from PKU who consumed the composition of Wachtel would only have to consume half the daily dosage when compared to the prior known amino acid mixtures. This would then lead to better compliance by patients and thus a higher chance of a proper, long-term diet.

However, Wachtel did not prove to be a promising springboard for the invention claimed in the present application, more than 13 years after the publication of Wachtel.

As explained in the present specification beginning at page 28, line 18, the aim of the present invention is quite different. In particular, the presently claimed invention provides an alternative and improved PKU treatment compared to the prior art treatments, in which the claimed supplement - as opposed to a diet - reduces the uptake of Phe from a normal food

intake or a Phe-low diet.

Thus, Wachtel provides a Phe-poor diet with optimal nutritional make-up and optimal acceptance by the patient in a life-long diet, while the present invention relates to novel LNAA supplements with improved efficiency in the treatment of PKU patients.

Wachtel does not teach or suggest modifying its composition in order to obtain a better - i.e. therapeutically more effective - composition for the treatment of PKU.

In summary, Applicant respectfully submits that Wachtel does not point to anything which is related to the aim of the present invention (i.e. an improved supplement for PKU patients). Wachtel does not disclose a supplement permitting a PKU patient to have an otherwise normal food intake, but instead teaches a composition which substitutes for a normal diet. A person of ordinary skill in the art would not have used Wachtel as springboard for developing a LNAA mixture for use as a *supplement* to the normal food intake or diet for PKU patients in order to further reduce Phe and its toxic metabolites in the brain. Thus, nothing in Wachtel would lead the skilled person to the presently claimed invention.

Applicant submits that the technology of Pietz et al., which is described in the present specification beginning on page 28 ("Pietz") should be considered as more pertinent prior art than Wachtel. Pietz's work formed the theoretical basis for the commercial product Prekunil®, with which supplement mixtures according to the claimed invention were compared and found surprisingly better. Pietz is concerned with the same problem as the present invention (blocking Phe uptake into the brain) as the present invention.

Pietz relates to the testing of LNAA supplements and how they block Phe transport into the brain in patients with PKU. The aim of the study in Pietz was to use the approach to further investigate Phe transport through the blood brain barrier in the patients by manipulating blood concentrations of Phe as well as other LNAA's e.g. by giving an LNAA mixture comprising Val, Met, iLeu, Leu, Tyr, His and Trp. With supplement of LNAA's, Pietz observed that Phe influx into the brain was completely blocked. The research studies led to the development of Prekunil®, the commercial LNAA supplement for treatment of PKU preceding the present invention. (Information relating to Prekunil® is attached as Exhibit A).
Prekunil® is disclosed in the enclosed document.

The purpose of the present invention is to provide an alternative and improved PKU treatment compared to the prior, commercially available treatment with Prekunil®. The solution provided by Applicant's invention is an LNAA dietary supplement as defined in claim 57, where Lys is added.

The present invention is designed to compete with and suppress transport of Phe from the GI tract into the blood and thereby to reduce the plasma Phe level. The more effective suppression using the presently claimed supplement results from the addition of Lys and is verified by the test results in Table 6 of the present application. Thus, a reduction of 27% in Phe plasma level 6 hours post-dose has
been verified with the compositions of the invention, whereas the corresponding reductions in the control group and in the group treated with Prekunil are 13% and 18%, respectively.

Pietz does not in any way suggest modifying LNAA supplements like the commercial LNAA supplement, Prekunil®, with Lys in order to obtain an improved LNAA supplement for the treatment of PKU. A person of skill in the art would have had no reason to modify the commercial supplement, Prekunil®, to more effective alternatives by adding Lys.

Experts within PKU treatment have for many years been studying different ways and different amino acid supplements to make the treatment more effective, but without much success.

In view of the foregoing, Applicant respectfully submits that the presently claimed invention would not have been obvious over Wachtel or any other art, and requests withdrawal of the rejection under § 103(a).

Conclusion

Applicant believes the currently pending claims are now in condition for allowance. If the Examiner has any questions regarding this response, the Examiner is invited to telephone Applicant's counsel at the number provided below.

Respectfully submitted,
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